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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,037	01/19/2005	Klaus Michael Debatin	085449-0152	6277

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EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,037	DEBATIN ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *23-44* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Debatin et al.

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 23-34 and 44, drawn in part to a Smac protein/carrier entity, a drug containing an entity as specified in claim 31, optionally in combination with at least one active apoptosis-inducing or proliferation-inhibiting compound and a pharmaceutical carrier, wherein the active compound is a cytostatic compound, a medicament for the treatment of cancer.

Group II, claim(s) 23-31, 35-37 and 44, drawn to drawn in part to a Smac protein/carrier entity, a drug containing an entity as specified in claim 31, optionally in combination with at least one active apoptosis-inducing or proliferation-inhibiting compound and a pharmaceutical carrier, wherein the active compound is a death receptor ligand, a medicament for the treatment of cancer.

Group III, claim(s) 23-31, 38-40 and 44, drawn in part to a Smac protein/carrier entity, a drug containing an entity as specified in claim 31, optionally in combination with at least one active apoptosis-inducing or proliferation-inhibiting compound and a pharmaceutical carrier, wherein the active compound is an antibody against a death receptor, a medicament for the treatment of cancer.

Group IV, claim(s) 41-43, drawn to a method of treating cancer in a human or an animal comprising administering of a Smac/carrier entity, optionally in combination with at least one active apoptosis-inducing compound.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature linking the Groups I-IV appears to be the Smac/TAT or fragment thereof entity (see claim 24, for example). The Smac/TAT or fragment thereof entity cannot be a special technical feature under PCT Rule 13.2 because it is shown in the prior art. WO 02/16402 (Pub. Date: 2/28/2002) teaches a method of enhancing apoptosis of pathogenic cells comprising the step of contacting the cells with an effective amount of an AV peptoid, wherein the AV peptoid may be SMAC or fragment thereof (see claims and pages 27-28, example 9). Kueltzo et al. (Science, 1999, 285(3): 1569-1572) teach that delivery of therapeutic proteins into tissues and across the blood-brain barrier is severely limited by the size and biochemical properties of the proteins (see abstract). Kueltzo et al. teach a method of delivery of therapeutic proteins into all tissues including the brain by fusing the therapeutic protein to the protein transduction domain from the human immuno deficiency virus TAT protein. It would have been obvious to one skilled in the art to combine the teaching of WO 02/16402 and Kueltzo et al. to make a fusion protein of Smac/TAT or fragment thereof because by doing so the Smac protein or fragment thereof can be more efficiently delivered into any pathogenic cells. Therefore the technical feature linking the inventions is not novel and does not provide contribution over the prior art. Therefore, unity of invention is lacking and the inventions are deemed to be separate.

2. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

(i) *carrier*:

TAT, influenza virus hemagglutinin, the VP22 protein from herpes simplex virus, Antennapedia, fibroblast growth factor, Galparan (transportan), poly-arginine, and Pep-I.

(ii) *cytostatic compound*

antimetabolites, preferably cytarabine, fludarabine, 5- fluoro-2"-eoxyuiridine, gemcitabine, hydroxyurea or methotrexate; DNA-fragmenting agents, preferably bleomycin, DNA-crosslinking agents, preferably chlorambucil, cisplatin, cyclophosphamide or nitrogen mustard; intercalating agents preferably adriamycin (doxorubicin) or mitoxantrone; protein synthesis inhibitors, preferably L-asparaginase, cycloheximide, puromycin or diphteria toxin; topoisomerase I poisons, preferably camptothecin or topotecan; topoisomerase II poisons, preferably etoposide (VP-16) or teniposide; microtubule-directed agents, preferably colcemid, colchicine, paclitaxel, vinblastine or vincristine; kinase inhibitors preferably flavopiridol, staurosporin, STI571 (CPG 57148B) or UCN-01 (7-hydroxystaurosporine); miscellaneous investigational agents, preferably PS-341, phenylbutyrate, ET-18-OCH3, or famesyl transferase inhibitors

(L-739749, L- 744832); polyphenols preferably quercetin, resveratrol, piceatannol, epigallocatechine gallate, theaflavins, flavanols, procyanidins, betulinic acid; hormones preferably glucocorticoids or fenretinide; hormone antagonists, preferably tamoxifen, finasteride or LHRH antagonists; plant-derived cytostatics (from Viscum and derivatives); alcaloids preferably vindesine; podophyllotoxins preferably vinorelbin; alkylants preferably nimustrine, carmustrine, lomustine, estramustrine, melphalam, ifosfamide, trofosfamide, bendamustine, dacarbazine, busulfane, procarbazine, treosulfane, tremozolamide, thiotepa; cytotoxic antibiotics preferably aclarubicine, daunorubicine, epirubicine, idarubicine, mitomycine, dactinomycine; antimetabolites like folic acid analogs preferably methotrexate, purine analogs preferably cladribin, mercaptopurin, tioguanine and pyrimidine analogs preferably cytarabine, fluorouracil, docetaxel; other antineoplastic, platinum compounds preferably thioplatin, carboplatin, oxaliplatin; amsacrine, irinotecane, interferon-a, tretinoine, hydroxycarbamide, miltefosine, pentostatine, aldesleukine; antineoplastic compounds derived from organs, e.g. monoclonal antibodies preferably trastuzumab, rituximab, or derived from enyzmes preferably pegaspargase; endocrine effecting antineoplastic compounds belonging to hormones, e.g. estrogens preferably polyestradiol, fosfestriol, ethinylestradiol, gestagens preferably medroxyprogesterone, gestonoroncaproat, megestrol, norethisterone,

lynestrenol, hypothalamus hormones preferably triptoreline, leuproreline, busereline, gosereline, other hormones preferably testolactone, testosterone; endocrine effecting antineoplastic compounds belonging to hormone antagonists, e.g. antiestrogens preferably toremifen; antiandrogens preferably flutamide, bicalutamide, cyproterane; endocrine effecting antineoplastic compounds belonging to enzyme inhibitors preferably anastrol, exemestane, letrozol, formestane, aminoglutethimide, all of which can be occasionally administered together with so-called protectives preferably calciumfolinat, amifostin, lenograstin, molgromostin, filgrastin, mesna or so-called additives preferably retinolpalmitate, thymus D9, amilomer.

(iii) death receptor ligand

tumor necrosis factor α (TNF-α), tumor necrosis factor β (TNF-β, lymphotoxin-α), LT-β (lymphotoxin-β), TRAIL (Apo2L), CD95 (Fas, APO-1) ligand,TRAMP (DR3, Apo-3) ligand, DR4 ligand, DR6 ligand.

(iv) antibody

anti-CD95 antibody, anti-TRAIL-R1 (DR4) antibody, anti-TRAIL-R2 (DRS) antibody, anti-DR6 antibody, anti TNF-R1 antibody and anti-TRAMP (DR3) antibody.

(v) cancer

neuroblastoma, rectum carcinoma, colon carcinoma, familiary adenomatous polyposis carcinoma, hereditary non-polyposis colorectal

cancer, esophageal carcinoma,labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tong carcinoma, salivary gland carcinoma, gastric arcinoma, adenocarcinoma, medullary thyroidea carcinoma, papillary thyroidea carcinoma, renal carcinoma, kidney parenchym carcinoma, ovarian carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, pancreatic carcinoma, prostate carcinoma, testis carcinoma, breast carcinoma, urinary carcinoma, melanoma, brain tumors preferably glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), acute myeolid leukemia (AML), chronic myeloid leukemia (CML), adult T-cell leukemia lymphoma, hepatocellualar carcinoma, gall bladder carcinoma, bronchial carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroidea melanoma, seminoma, rhabdomyosarcoma, craniopharyngeoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma and plasmocytoma.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims

subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

4. The claims are deemed to correspond to the species listed above in the following manner:

Carrier:	claim 1
Cytostatic compound:	claims 33 and 34.
Death receptor ligand:	claims 35 and 36
Antibody:	claims 39 and 40
Cancer:	claims 42

The following claim(s) are generic: none.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: the special technical feature liking the species in group (i) is a carrier. The carrier such as TAT is known in the art as shown by Kueltzo et al. (Science, 1999, 285(3): 1569-1572). The special technical features linking the species in Group (ii)-(v) are cytostatic compound, death

receptor ligand, antibody and cancer, respectively. However, cytostatic compound, death receptor ligand, antibody and cancer are all well known in the art. Therefore the technical feature linking the inventions is not novel and does not provide contribution over the prior art. Therefore, unity of invention is lacking and the species are deemed to be separate.

5. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

7. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang, Ph.D.
Art Unit 1643
Dec. 7, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER